Effects of parecoxib on patients' perception of analgesia and blood loss following open prostatectomy: a multicentre randomized trial

Daniel Dirkmann¹, Harald Groeben², David L. Stahl³, Matthias Eikermann¹,³

¹ Klinik für Anästhesiologie und Intensivmedizin, Universität Duisburg-Essen, Universitätsklinikum Essen, Hufelandstrasse 55, 45144 Essen, Germany
² Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie, Kliniken Essen Mitte, Henricistrasse 92, 45136 Essen, Germany
³ Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

E-Mail Addresses: Daniel.Dirkmann@uk-essen.de
h.groeben@kliniken-essen-mitte.de
dstahl@partners.org
meikermann@rics.bwh.harvard.edu

Corresponding author: Dr. med. Daniel Dirkmann
Klinik für Anästhesiologie und Intensivmedizin
Universitätsklinikum Essen
Hufelandstraße 55, D-45122 Essen
Phone: +49 201 72384423
Fax: +49 201 7235949
E-Mail: Daniel.Dirkmann@uk-essen.de
Abstract

Background: This multi-centre, prospective, randomized, double-blind, placebo-controlled study was designed to test the hypotheses that parecoxib improves patients' perception of postoperative analgesia without increasing surgical blood loss following radical open prostatectomy.

Methods: 105 patients (64±7 years old) were randomized to receive either parecoxib or placebo with concurrent morphine patient controlled analgesia. Cumulative opioid consumption (primary objective) and the overall benefit of analgesia score (OBAS), the modified brief pain inventory short form (m-BPI-sf), the opioid-related symptom distress scale (OR-SDS), and perioperative blood loss (secondary objectives) were assessed.

Results: In each group 48 patients received the study medication until 48 postoperative hours and had complete data sets available. Parecoxib significantly reduced cumulative opioid consumption by 24% (43±24.1 mg versus 57±28 mg, mean±SD, p=0.02), translating into improved benefit of analgesia (OBAS: 2(0/4) versus 3(1/5.25), p=0.01), pain severity (m-BPI-sf: 1(1/2) versus 2(2/3), p<0.01) and pain interference (m-BPI-sf: 1(0/1) versus 1(1/3), p=0.001), as well as reduced opioid-related side effects (OR-SDS score: 0.3(0.075/0.5083) versus 0.4(0.2/0.833), p=0.03). Blood loss was significantly higher at 24 postoperative hours in the parecoxib group ((4.3 g/dl (3.6/4.9)) versus (3.2 g/dl (2.4/4.95), p=0.02)).

Conclusions: In elderly patients after major abdominal surgery, parecoxib significantly improves patients' perceived analgesia. However, parecoxib may increase perioperative blood loss. Future trials are needed to evaluate this further.

Trial registration: ClinicalTrials.gov Identifier: NCT00346268

Number of words: 215
Keywords

analgesics non-opioids, parecoxib, analgesics opioids, morphine, pain, postoperative pain
Background

Ineffective postoperative pain control still remains an unsolved problem [1], resulting in prolongation of hospital stay and increased hospital costs [2]. Individualized, procedure specific postoperative analgesia is being propagated in order to solve this issue [3]. However, despite of growing evidence that there are procedure specific differences in postoperative pain [4] available guidelines are generalized for most surgical procedures [3] and opioids are being used as the mainstay analgesic [5]. However, their use is associated with well known side effects, which may affect patient satisfaction, length of hospital stay, and increase cost of care, as well [6, 7]. Non-steroidal anti-inflammatory drugs (NSAIDs), decrease perioperative opioid consumption and opioid-related side effects. However, their use is associated with adverse events such as surgical bleeding and ulcer generation [8]. Selective cyclooxygenase-2 (COX-2) inhibitors have been propagated to be a safe alternative for several years. Parecoxib (a prodrug of valdecoxib) is a parenterally selective cyclooxygenase-2 (COX-2) inhibitor that reduces postoperative opioid consumption, following thyroid surgery [9], hernia repair [10], gynecological laparotomy [11], total hip [12] and knee arthroplasty [13], as well as spine surgery [14]. However, the use of parecoxib in cardiac surgery was associated with an increased incidence of cardiovascular events in at-risk patients [15, 16]. Furthermore, long-term use of two other COX-2 inhibitors (namely celecoxib and rofecoxib) is associated with an increased cardiovascular risk in large trials aiming on colorectal adenoma prevention [17, 18]. In addition, there are data suggesting that COX-2 inhibitors may increase perioperative blood loss in non cardiac surgery [12]. The discovery of the fraud in the publications by Reuben et al., and the subsequent retraction of 21 peer-reviewed articles on perioperative analgesia, raised additional severe concerns about what is still known about risks and benefits of COX-2 inhibitor
treatment [19] and the validity of review articles including such fraudulent data has been questioned [20]. Accordingly, it seems important to gather additional perioperative data to better define the risk-benefit ratio of COX-2 inhibitor treatment in a procedure-specific fashion.

The primary objective of this multi-center, prospective, randomized, double-blind, placebo-controlled study was to assess, the benefit of parecoxib analgesia in a collective of patients undergoing radical open prostatectomy. The secondary objective was to evaluate the effects of parecoxib on blood loss, as measured by the peri- and postoperative decrease in the serum hemoglobin concentration.
Methods

This investigator initiated, multi-centric, prospective, double-blind, placebo-controlled study was conducted in compliance with the ‘Declaration of Helsinki’ and according to ‘Good Clinical Practice’ guidelines, at three German hospitals. Patients were recruited between December 2006 and September 2010 when the study was prematurely terminated because of slow recruitment due to increasing use of roboter assisted surgery at all investigational centers. The study was funded by Pfizer, Germany and Pfizer was involved in the generation of the study design. However, Pfizer did not influence the interpretation and the discussion of results. The study was registered at www.clinicaltrials.gov (Identifier: NCT00346268). The study was reviewed and approved by the ethics committee of the University Duisburg-Essen (Ethik-Komission der Universität Duisburg Essen, Robert-Koch-Straße 9-11, 45147 Essen, Germany, protocol number: A3481066, date of approval 25.09.2006). All patients gave written informed consent.

Inclusion and exclusion criteria

We included patients aged ≥ 18 years scheduled for elective radical open prostatectomy with an American Society of Anesthesiologists (ASA) physical status of I or II, who did not have a high risk of developing an acute coronary event within the next 10 years, according to the Prospective Cardiovascular Münster Heart Study (PROCAM) [21]. Patients with congestive heart failure or established ischemic heart disease, peripheral and/or cerebrovascular arterial disease, or those with a history of coronary artery bypass graft (CABG) procedure were excluded. Additional exclusion criteria were a history of asthma or bronchospasm that required treatment with oral glucocorticoids, inflammatory bowel disease, chronic or acute renal or hepatic disease, coagulopathy, and adverse
events after previously taking acetylsalicylic acid, NSAIDs. We did not include patients with active or suspected gastrointestinal ulceration or bleeding, or a history of alcohol, analgesic, or narcotic abuse. Furthermore, individuals with known laboratory abnormality of aspartate aminotransferase (AST) or serum glutamic oxaloacetic transaminase [SGOT]) or alanine aminotransferase (ALT) or serum glutamic pyruvic transaminase [SGPT]) greater than 1.5 times the upper limit normal, or creatinine greater than 1.5 times the upper limit of normal were excluded. Finally we excluded patients on antidepressants, hypnotics, opioids, NSAIDs, antihistamines, anxiolytics, sedatives, systemic corticosteroids if the drugs were given during the 24 hours prior to surgery, except for routine preoperative anxiolytic medication. Long-acting NSAIDs (e.g., oxaprozin, piroxicam), acetylsalicylic acid, or other anti-platelet drugs were stopped 7 days before the first dose of study medication.

Prior and Concomitant Medications and Procedures

On the preoperative evening all subjects received dikaliumclorazepate (Tranxilium) 20 mg by mouth for sedation. On the preoperative morning all subjects received midazolam (Dormicum) 7.5 mg orally for anxiolysis.

All patients received general anesthesia, and the general anesthesia plan was left to the discretion of the individual anesthesiologist. No patients received neuraxial analgesia. After removal of the prostate via open prostatectomy and placement of the urinary catheter at least one drain was placed in the perivesical space. At the end of the operation patients were extubated and transferred to the intensive- or intermediate-care-unit for monitoring until the next morning. No oral fluid intake was allowed on the day of surgery, but crystalloid was given IV (up to 3.000 mL). In the evening of the operative day all subjects received enoxaparin 20 mg as thrombembolism prophylaxis. If requested,
patients could receive dikaliumclorazepate (Tranxilium) up to 20 mg/d.

**Randomization and blinding**

Subjects were randomized according to a specific identification, which had been assigned at the preoperative visit, upon arrival at the post-anesthesia care unit (PACU). The clinical site’s pharmacist or authorized site personnel allocated the subject into either the parecoxib or the placebo arm using a computer generated random list. In order to preserve the double-blind assignment, treatments were prepared by a third person not being involved in the evaluation of subjects. All study medications were administered as a clear solution using 2 ml syringes.

**Study medication and rescue analgesia**

The first dose of the study medication (parecoxib 40 mg or placebo) was administered upon patients’ arrival in the PACU by the anesthesiologist. Subsequent doses of the study medication (parecoxib 20 mg or placebo) were administered by a study staff nurse every 12 hours (± 1 h) until postoperative day 2 (48 ± 1h) after skin closure. Patients received patient controlled analgesia using morphine (1 mg/ml) for postoperative analgesia with the following setting: no continuous infusion, bolus-dose 1 mg, lock-out time 10 min, 4-h dose limit 40mg).

**Measurements**

All subjects underwent scheduled visits 24 (± 1 h) and 48 (± 1 h) hours, after receiving the first dose of the study medication. Opioid consumption and all items needed to calculate the Overall Benefit of Analgesic Score (OBAS), the modified-brief pain inventory-short form (m-BPI-sf) (pain perception (pp) score and pain interference (pi)
score), and the opioid-related symptom distress scale (OR-SDS) were assessed.

We developed and validated the OBAS by using pain scores, opioid consumption, as well as the m-BPI-sf, and OR-SDS, previously [22]. The OBAS combines measurements of pain intensity, opioid related adverse events, and also patients’ satisfaction (global evaluation). Accordingly, we believe it is an important outcome variable that reflects a patient’s subjective benefit from postoperative multimodal pain therapy.

Furthermore, we measured the intra- and postoperative decrease in serum hemoglobin concentration (Hb) and transfusion requirements intraoperatively and during 48 hours following skin closure [23]. More specifically, intra operative blood loss was defined as: \([\text{Hb } g/dL]\text{pre} - [\text{Hb } g/dL]\text{post} + \text{intraOP RBCU}\); where \((\text{Hb } g/dL]\text{pre}\) is the blood hemoglobin concentration preoperatively, \((\text{Hb } g/dL]\text{post}\) is the blood hemoglobin concentration assessed postoperatively, and \text{intraOP RBCU}\) is the number of red blood cell units (RBCU) substituted during prostatectomy. Furthermore, we calculated the total blood loss as: \([\text{Hb } g/dL]\text{pre} - [\text{Hb } g/dL]\text{@48} + \text{RBCU during 48 hours}\); where \((\text{Hb } g/dL]\text{pre}\) is the blood hemoglobin concentration preoperatively, \((\text{Hb } g/dL]\text{@48}\) is the blood hemoglobin concentration 48h after skin closure, and \text{RBCU during 48 hours}\) is the number of red blood cell units (RBCU) substituted after prostatectomy until 48h after skin closure. Total blood loss at 24 postoperative hours was calculated similarly. However, as there were no data available for RBCU transfused during the first 24 hours calculations did not account for transfusions.

Serious adverse events were monitored by daily chart review, and by interviewing the Urologist in charge for this study, in order to monitor for perioperative myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, and gastrointestinal or surgical bleeding.
Statistical Analysis

An a priori sample size calculation was performed using a two sided t-test and a type I error of 5%. Considering an estimated drop out rate of 15% and an expected reduction in morphine consumption by 25%, a total of 76 individuals per group was calculated to achieve a power of 80%.

All data were analyzed using Prism 5 for Mac OS X, Version 5.0d (Graph Pad Inc., La Jolla, California). Data were tested for normality using the Kolmogorov-Smirnov test with Dallal and Wilkonson approximation of the Lillifores method, when appropriate. Data were analyzed using t-test, Mann-Whitney-U test, or chi-squared test as noted below. If not stated otherwise data are shown as median (25th / 75th percentile).

Morphine consumption (primary), and blood-loss (secondary) during the first 48h, and variables on OBAS, m-BPI-sf score, and OR-SDS taken at 48h after skin closure were compared between groups using Mann-Whitney-U-test.

We applied a multiple regression analysis model using postoperative decrease in hemoglobin concentration as the dependent variable and included independent variables that we considered might affect postoperative blood loss during parecoxib therapy: age, activated partial thromboplastin time (aPTT), Quick, platelet count, test drug.

The incidence of adverse events was compared between groups using chi-squared tests.
Results

Patients
A total of 105 patients (52 parecoxib, 53 placebo) were enrolled in this trial and received treatment. Of these subjects, 96 patients (48 parecoxib, 48 placebo) received the study medication until 48 postoperative hours and had complete data sets available. One patient had to be excluded for protocol violation, another due to an adverse event (hyperhydrosis, parecoxib group), and three patients had to be excluded because of withdrawal of consent (placebo group). Two patients from each group had to be excluded since relevant data were missing (Figure 1). Of the patients included in the final analyses, 34 (17 receiving parecoxib) were recruited at investigational center one, 60 patients (31 receiving parecoxib) at investigational center two, and two patients (both receiving placebo) were recruited at investigational center three. The physical characteristics and laboratory variables were comparable in both groups (Table 1).

Efficacy
Mean morphine consumption was lower (24.4%) during the first 48 postoperative hours following surgery in subjects receiving parecoxib (43.1 ± 24.1 mg) (mean±SD) as compared to those receiving placebo (57.1 ± 28 mg, p=0.02) (Figure 2). Parecoxib administration resulted in a significantly decreased OBAS at 48 hours after the first administration (2 (0/4)) as compared to the placebo group (3 (1/5.25)) (p=0.01) (Figure 3A). Values of Opioid Related-Symptom Distress Scale (OR-SDS) were lower in patients receiving parecoxib, (0.3 (0.075/0.5083)) compared to the placebo group (0.4 (0.2/0.833)) (p=0.03) (Figure 3B).
Calculation of the pain severity (ps) and the pain interference (pi) scores of the Modified-Brief Pain Inventory-Short Form (m-BPI-sf) revealed that parecoxib was effective in
reducing patients pain severity (1(1/2) versus 2(2/3), p<0.01) (Figure 3C) as well as pain interference with patients life (1(0/1) versus 1(1/3), p<0.01) (Figure 3D).

**Blood loss and transfusion requirements**

Intraoperative decrease in Hb was similar in both groups (p=0.26). Median decrease in Hb was 3.2 g/dl (2.1/3.7) in the parecoxib group and 2.3 g/dl (1.7/3.8) in the placebo group. Decrease in Hb during the first 24 hours following skin closure was significantly greater in the parecoxib group (4.3 g/dl (3.6/4.9)) as compared to the placebo group (3.2 g/dl (2.4/4.95) (p=0.02) (Figure 4).

Multiple regression analysis using decrease in Hb assessed at 24 hours postoperatively as the dependent variable and age, activated partial thromboplastin time (aPTT), Quick, platelet count, and test drug as independent variables confirmed that the test drug (i.e. parecoxib or placebo) was the only independent factor associated with higher decrease in Hb during 24 hours, postoperatively (p=0.026). Data on the variables included are listed in table 1. However, the effect was no longer statistically significant when analyzing the decrease in Hb at 48 hours. The median decrease in Hb was 4.4 g/dl (3.8/5.4) in the parecoxib group and 3.85 g/dl (2.8/5.4) in subjects receiving placebo (p=0.1183) (Figure 4).

Transfusion requirements were similar between groups. One patient from each group had 1 RBCU transfused within the first 48 hours following skin closure. Four subjects from the parecoxib group and 1 subject from the placebo group had 2 RBCU transfused within the first 48 hours after surgery.
Adverse events

All patients were included in the analyses of safety. Throughout the study period, a total of 116 adverse events (AEs) were observed in 43 subjects (83%) in the parecoxib group and 109 AEs in 42 subjects (79%) in the placebo group, respectively. The most common adverse events, occurring in 2 or more subjects are listed in table 2. There were no statistical differences in the frequencies of the listed adverse events between the treatment and the placebo group, respectively, as determined using a Fishers exact test. Most adverse events were classified mild (n=156) to moderate (n=62) in both groups. However, serious or severe adverse events (n=7) were reported for two subjects (thrombocytosis and hyperhidrosis) in the parecoxib group and 5 subjects (diarrhea, pyrexia, confusional state, and hemorrhage) in the placebo group. Only one patient in the parecoxib group discontinued treatment, secondary to severe hyperhidrosis, which started 20 minutes after receiving the study drug. Of the adverse events in the parecoxib arm, a total of three (hypokalemia, acute renal failure, and hyperhidrosis) were classified as being treatment related.
Discussion

The results of this study indicate that postoperative parecoxib treatment in patients undergoing radical open prostatectomy decreases morphine consumption and improves the quality of pain relief. However, our study also suggests that parecoxib use in patients undergoing radical open prostatectomy may be associated with increased perioperative blood loss.

The efficacy of analgesic drugs for postoperative analgesia is considered to be procedure specific [24] and most studies focus on the reduction of opioid requirements as their primary outcome measure [8]. In our present study, parecoxib analgesia resulted in an average reduction of cumulative morphine requirements by 24% compared to placebo, in patients undergoing open prostatectomy. This finding is in accordance with previous studies describing an opioid sparing effect of COX-2 inhibitors in the postoperative period.[9-14] However, opioid sparing is not, by itself, considered a clinically meaningful endpoint.[8, 25] Accordingly, our study examined other measurements assessing patients’ benefits from multimodal analgesia. Furthermore, most studies assess the incidence of adverse events but seldom use well established, validated scores like the OR-SDS or the pain interference score derived from the m-BPI-sf [26]. Since both, pain related symptoms and opioid related side effects are associated with patient satisfaction [27] we performed additional assessment of the OBAS which we developed and validated recently. As demonstrated, the OBAS correlated much better with patient satisfaction than analyzing pain scores alone. Furthermore, the OBAS yields higher resolution of analgesic treatment effects of COX-2 inhibitors than pain scores, OR-SDS and m-BPI-sf [22]. In the present study, the opioid sparing effect of postoperative parecoxib translated into a significant reduction of OBAS, OR-SDS, and m-BPI-sf scores, indicating that patients perceived significant benefit from parecoxib, namely reduced pain intensity, reduced opioid
associated side effects, and less interference with their lives. These findings are in accordance with other studies assessing OR-SDS and/or m-BPI scores [14, 28, 29] and indicate that opioid sparing effects of non-opioid analgesics may translate into clinical benefit in patients perception of analgesia.

In our study, the postoperative use of parecoxib was not associated with increased bleeding, as measured as the total blood loss at 48 postoperative hours, as specified a priori. However, there was a trend towards higher blood loss at this predefined time interval and a trend towards higher transfusion requirements (5 patients in the parecoxib group vs. 2 patients in the placebo group receiving any RBCU transfusion). Furthermore, the incidence of postoperative anaemia was 1.5 times higher in patients receiving parecoxib. However, this difference was not found statistically significant. In addition, analyses of the postoperative decrease in Hb revealed a higher decrease in Hb in patients receiving parecoxib during the first 24h following surgery compared to placebo. The lack of statistical significance in the total blood loss at 48 postoperative hours might be due to the relatively small size of the study population. While use of classical NSAIDs is associated with approximately six times as many surgical bleeding complications (2.4%) compared to placebo (0.4%), according to a recent meta analysis [30] COX-2 inhibitors are generally considered not to increase blood-loss. However, a trend towards an increased incidence of postoperative anemia associated with parecoxib (14.1% vs. 10%) has been reported previously [12]. Although, the latter data by Malan et al.,[12] as well as our data lack statistical significance, we believe that such increase in the incidence of postoperative anemia and transfusion requirements has to be considered clinically relevant and should prompt further research.

How can we explain a potential effect of COX-2 inhibitors on postoperative blood loss? In contrast to traditional NSAIDs, COX-2-inhibitors do not affect platelet aggregation, as
shown by impedance aggregometry, thromboelastometry, and platelet function analyzer (PFA-100) assays [31, 32]. Nevertheless, COX-2 inhibitors may also increase blood loss via drug interactions [33, 34]. Parecoxib and its metabolite valdecoxib are suspected to potentiate warfarin’s effects since both COX-2 inhibitors exert inhibitory effects on CYP2C9,[35] an enzyme that also metabolizes warfarin. Comedication with warfarin and parecoxib has been shown to increase the propensity to bleeding [35]. In addition, we speculate that it might be possible that COX-2 inhibitors, similar to aspirin [36] may affect fibrinolysis and that increased blood loss might be procedure-specific [37].

However, our data regarding blood loss have to be interpreted cautiously. First of all our study was designed to assess blood loss at 48 hours not as a primary, but as a secondary outcome measure. Accordingly, the study was originally powered based on the expected opioid sparing effect. Future trials should be powered to detect differences in blood loss and should consider procedures with a considerable bleeding risk. Accordingly, given our data (secondary endpoint and exploratory data) in line with the observation of others [12] we feel that the effects of COX-2 inhibitors on blood loss needs to be further evaluated in future in trials.
**Conclusions**

In summary, our data show that the perioperative use of parecoxib for adjunctive analgesia following open prostatectomy is associated with significant opioid sparing that translates into clinical analgesic benefit to patients. However, parecoxib may increase perioperative blood loss.
Competing interests

The study was funded by Pfizer, Germany and Pfizer was involved in the generation of the study design. However, the authors attest that Pfizer did not influence the interpretation and the discussion of results.

Harald Groeben and Matthias Eikermann received funds from Pfizer for an investigator initiated trial. Daniel Dirkmann and David L. Stahl have no interest to declare.
Authors’ contributions

DD analyzed the data and wrote the manuscript. HG participated in patient recruitment and data collection and co-wrote the manuscript. DLS co-wrote the manuscript. ME designed the study, co-analyzed the data and wrote the manuscript.
References


Table 1 Descriptive data

<table>
<thead>
<tr>
<th></th>
<th>Parecoxib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>52</td>
<td>53</td>
</tr>
<tr>
<td>Subjects excluded</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.4 (±7.5)</td>
<td>65.0 (±7.2)</td>
</tr>
<tr>
<td>Age (years) range</td>
<td>47-83</td>
<td>46-75</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>14.5 (±1.2)</td>
<td>14.5 (±1.5)</td>
</tr>
<tr>
<td>aPTT (s.)</td>
<td>30 (±3.3)</td>
<td>30.1 (±3.6)</td>
</tr>
<tr>
<td>Quick (%)</td>
<td>100 (88 / 100)</td>
<td>97.5 (94 / 10)</td>
</tr>
<tr>
<td>Platelet count (x10⁹/L)</td>
<td>244 (±62)</td>
<td>224 (±56)</td>
</tr>
</tbody>
</table>

Data are given as numbers, mean (± standard deviation), or median (25th / 75th percentile), as appropriate. There were no significant differences between groups.
Table 2 Incidence of adverse events

<table>
<thead>
<tr>
<th></th>
<th>Parecoxib (n=52)</th>
<th>Placebo (n=53)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>6 (12)</td>
<td>4 (8)</td>
<td>0.53</td>
</tr>
<tr>
<td>Vertigo</td>
<td>0 (0)</td>
<td>3 (6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>0.36</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (4)</td>
<td>7 (13)</td>
<td>0.16</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (8)</td>
<td>8 (15)</td>
<td>0.36</td>
</tr>
<tr>
<td>Flatulence</td>
<td>6 (12)</td>
<td>10 (19)</td>
<td>0.42</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (23)</td>
<td>16 (30)</td>
<td>0.51</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (17)</td>
<td>4 (8)</td>
<td>0.15</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (2)</td>
<td>4 (8)</td>
<td>0.36</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8 (15)</td>
<td>7 (13)</td>
<td>0.79</td>
</tr>
<tr>
<td>Wound infection</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hypokaliemia</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>0.24</td>
</tr>
<tr>
<td>Confusion</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>0.5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>0.36</td>
</tr>
<tr>
<td>Bladder pain</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>0.5</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>0.62</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>0.68</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Condition</td>
<td>Parecoxib</td>
<td>Placebo</td>
<td>p-value</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (12)</td>
<td>4 (8)</td>
<td>0.53</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Lymphocele</td>
<td>6 (12)</td>
<td>2 (4)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

There were no differences in the incidence of adverse events between parecoxib and placebo. Results are given as numbers (%) of patients reporting an adverse event.
Figure legends

Figure 1
Patient flow chart

Figure 2
Cumulative amount of morphine used at 48 hours following skin closure. Box-plots of quartiles (boxes), median (line within box), minimum, and maximum (error bars). Morphine consumption was significantly less in the parecoxib group vs. placebo.

Figure 3
Variables of analgesic efficacy at 48 hours following skin closure. OBAS (A), OR-SDS score (B), m-BPI-sf pain perception score (C), and m-BPI-sf pain interference score (D). Box-plots of quartiles (boxes), median (line within box), minimum, and maximum (error bars). All measurements of analgesic efficacy were significantly less in the parecoxib group vs. placebo.

Figure 4
Decrease in hemoglobin concentration (Hb) measured as: \([\text{Hb g/dL}]_{\text{prä}} - [\text{Hb g/dL}]_{@48} + \text{RBCU during 48 hours}\); where \([\text{Hb g/dL}]_{\text{prä}}\) is the blood hemoglobin concentration preoperatively, \([\text{Hb g/dL}]_{@48}\) is the blood hemoglobin concentration 48h after skin closure, and RBCU during 48 hours is the number of red blood cell units (RBCU) substituted after open prostatectomy until 48h after skin closure. Box-plots of quartiles (boxes), median (line within box), minimum, and maximum (error bars). Decrease in Hb was significantly higher in the parecoxib group vs. placebo.
Enrollment

Assessed for eligibility (n=116)

Excluded (n=6)
- Not meeting inclusion criteria (n=5)
- Other reasons (n=1)

Randomized (n=105)

Allocation

Allocated to placebo (n=53)
- Received allocated intervention (n=53)

Allocated to parecoxib group (n=52)
- Received allocated intervention (n=52)

Follow-Up

Discontinued intervention (n=3)
- No longer willing to participate (n=3)

Discontinued intervention (n=2)
- Adverse event (n=1)
- Protocol violation (n=1)

Analysis

Analysed (n=50) (adverse events)
- Excluded from analyses of pain-scores and blood loss because of incomplete data (n=2)

Analysed (n=50)
- Excluded from analyses of pain-scores and blood loss because of incomplete data (n=2)
Figure 2

* p = 0.0243

Morphine consumption (mg)

Parecoxib

Placebo
Figure 3